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10/534,535	09/08/2005	Mara Rossi	272008US0PCT	7168

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OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
STOICA, ELLY GERALD	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/534,535	ROSSI, MARA	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

1. In the amendment filed 04/092008 Applicant cancelled all the initially pending claims 1-9, and added new claims 10-25 by reformatting claims 1-9. Claims 10-25 are pending and are currently examined.

New claim rejections necessitated by amendment

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 10-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaberc-Porekar et al. (J. Biochem. Biophys. Meth. 49, 335-360, 2001-cited by the Applicant) in view of Hauptmann et al. (U.S. Pat. No. 6,271,346) and in further view of Staples et al. (U.S. Pat. No. 5,169,936).

The new claims 10-25 are essentially a rewriting of the claims 1-3 (and by extension 4-9) such as they have proper dependencies and clearer language. As such, the rationale for rejection of the initial claims 1-3 is valid for the newly presented claims 10-25. The claims are drawn to a method of isolation and purification of TNF-binding proteins by Immobilized Metal Affinity Chromatography (IMAC) using copper as metal. The elution from the IMAC column is carried out at a pH comprised between 2.8 and 3.2. The recovered the h-TBP- 1, is applied on an Ion Exchange Chromatography (IEC) at an acidic pH, followed by an ion exchange chromatography at a basic pH (between 8 and 10); and further polished by an Hydrophobic Interaction chromatography step.

Gaberc-Porekar et al. teach that IMAC holds a number of advantages over biospecific affinity chromatographic techniques, which have a similar order of affinity constants and exploit affinities between enzymes and their cofactors or inhibitors, receptors and their ligands or between antigens and antibodies. The benefits of IMAC-ligand stability, high protein loading, mild elution conditions, simple regeneration and low cost- are decisive when developing large-scale purification procedures for industrial applications (p. 336, lines 1-6). The metal used in the metal-chelated affinity support can be Cu (II) (p. 336, last paragraph). Elution of the protein from the column is achieved by protonation with an elution buffer of lower pH and containing between 0.1-1M NaCl (p.337, last paragraph) (and thus responding to the limitations of claims 12 and 20). The authors also teach that, due to the fact that with every IMAC column some leaching of metal ions occurs, in the purification strategy IMAC is usually the first chromatographic step, followed by several polishing steps (p. 352, subheading 7.2).

Moreover, Gaberc-Porekar et al. teach the actual protein retention in IMAC is based primarily on the availability of histidyl residues. However, aromatic side chains of Trp, Phe and Tyr appear to contribute towards retention, if they are in the vicinity of accessible histidine residues (p.337lines 8-12 and Fig. 1). Since applicant did not provide an actual amino acid Seq. Id. for the protein claimed, but rather claimed it as the sequence between amino acids 20 and 180 of the recombinant h-TBP-1 (recombinant, extracellular, soluble fragment of human TNF Receptor-I, comprising the amino acid sequence corresponding to the 20- 29 180 amino acids fragment of Nophar et al. EMBO J., 9, 3269-3278, 1990, cited by Applicant). The same sequence is also a fragment of the soluble extracellular domain of the TNF R1 (studied by Naismith et al., Structure, 4, 1251-1262, 1996-where the crystal structure is revealed) and the UniprotKB/Swiss-Prot database entry P194438. In order to facilitate the interpretation of the teachings Gaberc-Porekar, the following table, making the correspondence between the numbering of the residues for the same protein in three evidentiary references is presented

Amino acid	# per Nophar et al.	# per P194438	# per Naismith et al.
H	42	63	34
Y	46	47	38
Y	48	69	40
F	68	89	60
H	74	95	66
H	77	98	69
Y	111	132	103

H	113	134	105
Y	114	135	106
W	115	136	107
F	120	141	112
H	135	156	127
H	148	169	140
F	151	172	143
F	152	173	144

According to the table, it is noted that, out of a total of 160 amino acids of the claimed polypeptide, 15 (i.e. >9%) are amino acid residues that have affinity towards the metal column used for IMAC. A cursory analysis of the Fig. 1 of the Naismith et al. reveals that the residues presented in the table are at the surface of the protein and thus accessible for interaction with the Cu (II) of the IMAC column. A similar conclusion can be drawn by inspecting the text regarding the structural feature of the SwissProt entry P194438, which shows the residues that are part of a beta strand and most of the residues in the table are not part of an organized structure but part of loops between the structures, i.e. exposed to the surface of the protein. Thus, the protein had a multitude of contact points accessible for interaction with the copper column.

Gaberc-Porekar et al. is silent about the actual pH value for elution and about the purification of a TNF binding protein using their method.

Hauptmann et al. teaches preparation of highly purified TNF-binding protein (TBP-1) from dialyzed urine from uremia patients by a combinations of steps comprising Ion exchange chromatography at a pH 8, affinity chromatography with on a rTNFα Sepharose column eluted with 0.2 M glycine/HCl, pH 2.5, followed by a polishing final step of reverse phase chromatography (Hydrophobic Interaction Chromatography) (Example 1).

Staples et al. teach methods of protein purification using immobilized metal affinity resins containing copper as the immobilized metal (col. 5, lines 24-34). Staples et al. also teach that a common technique of eluting the proteins adsorbed on an immobilized metal affinity column is to lower the pH to 3 or 4 (col. 1 lines 45-46).

The IMAC offers the benefits underscored by Gaberc-Porekar et al. and the basic steps of the IMAC purification on copper containing resins were iterated by Staples et al. The use of an eluting step with a solution with a pH between 2.8 and 3.2 to ensure a complete removal of the bound TNF binding protein-1 from the copper resin would have been feasible, since Hauptmann et al. proved that hTBP-1 is stable and active even after an elution with a solution of pH 2.5. Therefore, it would have been obvious for a person of ordinary skill in the art at the time that the invention was made to take advantage of the IMAC methods as motivated by Gaberc-Porekar et al. and modify the sequence of purification steps of Hauptmann et al., in view of the teachings of Staples et al. with a reasonable expectation of success.

On page 5 of their remarks, Applicants argue that: "… while it is true that IMAC with copper was known, there was no way to know with a reasonable predictability of

success that h-TBP-1 would behave the way they did as shown in the example. That is, "until the inventors applied the human' TNF-1 to the IMAC procedure followed by Ion Exchange Chromatography (IEC) at an acidic pH, followed by an ion exchange chromatography at a basic pH as shown in the examples, there would be no way to know that it would reasonably work."

The arguments were carefully considered but not found persuasive because as iterated supra, the methods were already known and routine in the art. Further, applicants have provided neither fact nor evidence to support their assertion of unpredictability.

Moreover, Hauptmann even used some of the same techniques for purification of hTBP-1 used by applicants … There is no unexpected result produced by the Applicant. Clearly it would have been within the skills of a person of ordinary skill in the art to apply the known methods and routine optimization to purify hTBP-1 and thus the expected results would have been a product of scientific common sense and not an inventive step.

Conclusion

5. No claims are allowed.

6. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lorraine Spector/ Ph.D.

Primary Examiner, Art Unit 1647